REMARKS

The Office Action of March 20, 2002 has been carefully reviewed and this response addresses the Examiner's concerns. Claims 1-62 were pending in the application. Claims 1-28 and 57-59 stand rejected. Claims 1, 4, 6-14, 22, 23, 27, 28, and 57 are herein amended, and such claims effectively change dependent claims 2, 3, 5, 24-26, 58, and 59. Claims 15-21 have been canceled. Claims 63-65 have been added. No new matter has been added.

A requirement for restriction under 35 USC §121 was made in the present application. In the Office Action, the claims are restricted as follows:

> Group I. Claims 1-28 and 57-59 drawn to a pharmaceutical composition comprising amlodipine and an atorvastatin metabolite, classified in Class 514 subclasses 423 and 356.
>
> Group II. Claims 29-56 and 60-62, drawn to a method of treating heart diseases employing a pharmaceutical composition comprising amlodipine and an atorvastatin metabolite, classified in Class 423, subclasses 423 and 356.

A restriction requirement under 35 USC §121 based upon an election of species was also set forth. In the Office Action, Claims 29-56 and 60-62 were considered generic to a plurality of disclosed patentably distinct species comprising heart disorders or conditions.

In response, the applicant makes the following election. Applicant provisionally elects for examination, with traverse, the invention of the pharmaceutical composition comprising amlodipine and an atorvastatin metabolite, and identifies claims 1-28 and 57-59 and added claims 63-65, as readable thereon.

Applicants maintain that all of the claims of the present invention should be examined together since they are so closely related as to justify an examination of all the claims as a single invention as the fields of search would necessarily be co-extensive.

Claims 4-21 and 25-28 were objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous

claim. Claims 4, 6-14, 27, and 28 have been rewritten to overcome this rejection as to claims 4-21 and 25-28.

Claims 1 was objected to due to certain informalities. The informalities of independent Claim 1 have been corrected herein in accordance with the Examiner's suggestions. Specifically, the informal term "ATM" has been rewritten as "hydroxylated atorvastatin metabolite".

Claims 1-28 and 57-59 were rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent Claims 1, 22, and 57 have been amended to clarify the term "formulation agents" in accordance with the Examiner's suggestions and these claims reach the balance of claims 1-28 and 57-59. Therefore, these rejections are believed to be overcome.

Claim 57 has also been amended to more fully encompass the scope of the invention as disclosed in the present application.

Claims 1-28 and 57-59 were rejected under 35 USC §103(a) as being unpatentable over Davison et al. (U.S. Patent No. 4,879,303) and Bjorge et al. (U.S. Patent No. 5,385,929) in view of Jukema et al. and the Merck Index.

More specifically, the Office Action asserts that Davison et al. teach a pharmaceutical compound comprising amlodipine besylate useful in treating ischemic heart disease, Bjorge at al. teach a pharmaceutical composition comprising atorvastatin metabolite useful in inhibiting cholesterol synthesis, and that Jukema et al. teach "the addition of a calcium channel blocker (amlodipine) to HMG-CoA reductase inhibition therapy (pravastatin) act synergistically in retarding the progression of coronary atherosclerosis". The Office Action also notes that the Merck Index Therapeutic Category and Biological Activity Index lists atorvastatin as a HMG-CoA reductase inhibitor, asserting this would thereby make it obvious to one of ordinary skill in the art at the time the invention was made to employ amlodipine besylate with atorvastatin metabolites in a pharmaceutical composition. Applicant respectfully transverses this rejection, at least in respect of claims 1-14, 22-28, 57-59 and 63-65 as now amended.

Applicant unexpectedly found that a combination of amlodipine and atorvastatin metabolites produces a beneficial synergistic antioxidant effect and results in reduced

lipid peroxide formation (see page 4 of Applicant's specification at paragraph 14). This synergistic antioxidant effect is independent of the well-characterized effects of these drugs on calcium transport and cholesterol metabolism. This is in stark contrast to the combination of the calcium channel blocker, amlodipine, and other HMG-CoA reductase inhibitors examined by the Applicant in the in vitro tests described in the specification, including other statins such as lovastatin and mevastatin (see page 5 of Applicant's specification at paragraph 15). The Examiner's attention is specifically drawn to Figure 5 of Applicant's specification which clearly shows that the antioxidant effect of the combination of amlodipine and atorvastatin metabolite far exceeds any antioxidant effect of either amlodipine or atorvastatin metabolite separately or even any antioxidant effect of amlodipine in combination with other HMG-CoA reductase inhibitors.

None of the cited references teach, disclose or suggest the combination of amlodipine and atorvastatin metabolite in a pharmaceutical composition effective for the inhibition of lipid peroxidation in human low density lipoprotein or membrane lipid bilayers. The cited references also do not teach, disclose or suggest the combination of amlodipine and atorvastatin metabolite in a pharmaceutical composition having an antioxidant effect.

The Office Action admits that Davison et al. and Bjorge et al., taken together, do not teach a pharmaceutical composition as disclosed in the present application, but relies on the additional combination of Jukema et al. and the Merck Index for its conclusion.

However, Jukema et. al. is a retrospective metanalysis of a clinical investigation. It cautiously concludes that the addition of a calcium channel blocker (not necessarily amlodipine) to HMG-CoA reductase therapy (pravastatin) may act synergistically in retarding the progression of coronary atherosclerosis, but did not provide any experimental data in support of this hypothesis. This is different than the hypothesis that the combination of a calcium channel blocker with an HMG-CoA reductase inhibitor is of therapeutic advantage for cardiovascular disease, a hypothesis which is not supported by the metanalysis of the REGRESS trial presented by Jukema et al.

Instead, Jukema et al. states that patients receiving the combination of a calcium channel blocker with the HMG-CoA reductase inhibitor pravastatin did *not* experience fewer adverse clinical events as compared to patients that were not on calcium channel

blocker therapy with pravastatin. In fact, it was reported in the article that patients that were being simultaneously treated with both a calcium channel blocker and pravastatin actually had more cardiovascular complications (e.g., more revascularization procedures) than patients not taking the treatment combination. Although the increase in adverse events with the drug combination was not statistically significant, it further argues against a synergistic therapeutic benefit based on this retrospective nonexperimental analysis. Jukema et al. recognized the combination of a calcium channel blocker with pravastatin improved anatomical changes in certain coronary vessels, as measured with angiographic approaches, but this did not correlate with an improvement in clinical outcomes. This lack of an association between clinical benefit and angiographic changes in the coronary arteries with plaque development argues against a therapeutic advantage for cardiovascular disease. In fact, it is now accepted by those skilled in the art that changes in lumen size of the coronary artery (the parameter measured by angiography) do not effectively predict clinical outcomes with therapeutic intervention (see Levine et al., "Cholesterol Reduction in Cardiovascular Disease ", *New England Journal of Medicine*, 1995; **332**:512-521, attached hereto and tabbed as Appendix B). Further support for this concept comes directly from a more recent clinical research study involving amlodipine in which the investigators reported that treatment with this calcium channel blocker alone resulted in an impressive decrease in adverse vascular events, including hospitalizations, without any significant improvement in coronary artery lumen dimensions (Pitt et al. "Effect of Amlodipine on the Progression of Atherosclerosis and the Occurrence of Clinical Events", *Circulation*; 2000;**102**:1503-1510, attached hereto and tabbed as Appendix C). Indeed, it appears that coronary angiography, which visualizes only the arterial lumen, fails to show the full extent of vascular disease progression. The data indicate that a compensatory expansion in the overall artery during atherosclerotic plaque development results in only limited changes in lumen size, as confirmed by human autopsy studies (Glagov et al. "Compensatory Enlargement of Human Atherosclerotic Coronary Arteries", *New England Journal of Medicine;* 1987;**316**:1371-1375, attached hereto and tabbed as Appendix D). Because wall tension varies directly with radius, the biomechanical stresses experienced by smaller, nonobstructing atheroma actually exceed those experienced by high-grade stenosis, which yield a smaller lumen.

Additionally, as recognized by Jukema et al., the basis for the anatomical changes noted may be due to confounding factors and not directly to the combination treatment. In particular, patients who were on a calcium channel blocker were more likely to also be treated with long-acting nitrates. The greater use of nitrates (a common treatment for patients with coronary artery disease that improves vascular physiology) among calcium channel blocker users was highly significant ($p<0.0001$) as compared to patients not treated with a calcium channel blocker. Patients who were receiving calcium channel blocker treatment were different from other patients in other ways as well, including their history of certain cardiovascular events such as fewer cases of myocardial infarction ($p<0.04$). The presence of these confounding variables is due to the fact that Jukema et al. reviewed a study that was not designed to test the potential therapeutic benefit of combining a calcium channel blocker and HMG-CoA reductase inhibitor. Jukema et al. state that such a prospective trial must be conducted before a true assessment of this concept can be made.

Jukema et al. did not propose a benefit in combining any particular calcium channel blocker, such as amlodipine, with an HMG-CoA reductase inhibitor. In fact, the analysis failed to show an advantage for patients treated with a dihydropyridine calcium channel blocker (amlodipine or nifedipine) as compared to representative non-dihydropyridine calcium channel blockers (diltiazem or verapamil). The extent to which a benefit associated with the combination of a dihydropyridine-type calcium channel blocker and pravastatin may exist is clouded due to the confounding variables identified by Jukema et al. and cannot be determined from this type of retrospective study.

The Office Action further states, in part, states that the combination of agents known to be useful individually for the same purpose into a single combination useful for the very same purpose is prima facie obvious. Heart disease and its progression are the result of a complex series of interconnecting factors which continue to be studied by the medical community. The mere fact that amlodipine is conventionally employed in the treatment of heart disease and atorvastatin metabolite is conventionally known to be employed in the treatment of heart disease does not render it obvious that the combination of amlodipine and atorvastatin metabolite would be obvious to one skilled in the art. One (amlodipine) is a dihydropyridine-type calcium channel blocker and acts

upon one factor known to contribute to heart disease, while the other (atorvastatin metabolite) is a HMG-CoA reductase inhibitor and acts upon a different and separate factor known to contribute to heart disease. In the complex system of factors that combine to produce heart disease and contribute to its progression, the combination of an agent useful in acting against one factor could just as easily cancel out the usefulness of a second agent useful in acting against a separate factor.

The combination of amlodipine and atorvastatin metabolite would, at best, be an inappropriate "obvious-to-try" speculation. As discussed above, Jukema et al. only recognize that calcium channel blockers as a class of drugs, not necessarily amlodipine, appear to augment the beneficial effects of a particular HMG-CoA reductase inhibitor, pravastatin, with respect of anatomical changes in coronary vessels, but not in rates of adverse clinical events. Jukema et al. hypothesize about the mechanism by which this occurs, but do not teach, suggest or disclose a mechanism one skilled in the art could utilize to determine which calcium channel blockers could be used to augment the benefit of which HMG-CoA reductase inhibitors or lipid lowering agents.

The Office Action hypothesizes that since pravastatin and atorvastatin belong to the same chemical group of therapeutic statins, atorvastatin metabolites might have therapeutic effects similar to pravastatin. Using the same reasoning, it could be said that mevastatin and lovastatin, also belonging to the same therapeutic group as atorvastatin, should be expected to have therapeutic effects similar to atorvastatin metabolites. In fact, Applicant's experimentation and resulting data have shown that the combination of mevastatin or lovastatin with amlodipine does not result in the beneficial antioxidant effect of the combination disclosed in Applicant's invention, even thought these other statins are in the same therapeutic family as atorvastatin metabolite, and in turn that atorvastatin metabolite is a significant improvement compared to atorvastatin. Therefore, it can not be said that the combination of amlodipine and atorvastatin metabolite would be obvious to one skilled in the art, especially since the combination results in an antioxidant effect distinct from any effects on calcium transport and cholesterol metabolism.

All rejections having been met, it is believed that the application is in condition for allowance. Withdrawal of the restriction requirement and allowance of claims 1-14,

and 22-65 is requested. If the restriction requirement is maintained, then allowance of 1-14, 22-28, 57-59, and 63-65 is requested.

The Assistant Commissioner for Patents is hereby authorized to charge and deficiencies to or credit any overpayment to Deposit Account No. 03-2410, Order No. 2189-P01CIP.

In accordance with Section 714.01 of the M.P.E.P., the following information is presented in the event that a call may be deemed desirable by the Examiner:

Jerry Cohen (617) 854-4000

Respectfully submitted,

R. PRESTON MASON
Applicant

By: _____
Jerry Cohen
Reg. No. 20,522
Attorney for Applicant

Date: October 28, 2003
(previously filed on September 20, 2002)